REMARKS/ARGUMENTS

By the current amendment, claims 1, 4, and 31-38 are amended. Claim 30 has been canceled. Claims 39-40 have been added. No new matter has been added.

The courtesies extended to Applicant's representative by the Examiners at the interview held May 25, 2011, are appreciated. The reasons presented at the interview as warranting favorable action are incorporated into the remarks below and constitute Applicants' record of the interview.

Claims 1, 4, 6-12 and 30-38 were rejected under 35 U.S.C. 103(a) as being unpatentable over Monia et al. (US 2003/0087854) in view of Cappellan et al. (Nature Genetics, Vol. 23, September 1999), KSR International Co. v. Teleflex Inc., 550 U.S.--, 82 USPQ2d 1385 (2007), and an evidentiary reference of Sturla et al. (British Journal of Cancer (2003) 89, pages 1276 - 1284).

Claims 1 and 30, as amended, are directed to a method which comprises comparing the amount of FGFR3 protein detected in a bladder tissue or urine sample of an individual, with a first reference value from a subject without bladder transitional cell carcinoma, and a second reference value from a subject with advanced T2 bladder transitional cell carcinoma. As recited in claim 1, increased levels of FGFR3 protein relative to the first reference value are indicative of the presence bladder TCC, and increased levels of FGFR3 protein relative to said second reference value are indicative of bladder TCC at a stage which is less advanced than T2, i.e., Ta or T2. Thus, the claimed method compares the detected

amount of FGFR3 protein to two reference values, and thus identifies both the *presence* of bladder TCC, and the *severity* of bladder TCC.

Similarly, newly presented claim 39 recites a method comprising comparing the amount of FGFR3 protein detected in a sample of an individual with a first reference value from a subject without bladder transitional cell carcinoma, and a third reference value from a subject with Ta or T1 bladder transitional cell carcinoma. According to the method of claim 39, levels of FGFR3 protein which are greater than the first reference value and less than the third reference value are indicative of advanced T2 bladder TCC. Again, the method of claim 39 compares the detected amount of FGFR3 protein to two reference values, and thus identifies both the *presence* of bladder TCC, and the *severity* of bladder TCC.

Support for this amendment is found in the specification as originally filed. According to the specification, "[c]ompared to controls expression levels of *FGFR3* were increased more than 8-fold (SLR>3) in pTaG1 and pT1G3 carcinomas and more than 4–fold (SLR>2) in T2G3 carcinomas." *Page 19, ll. 5-8; Page 20, ll. 4-6.* The specification further states that "[e]levated levels of FGFR3 protein expression in cell membranes was predominantly associated with the Ta and T1 stages (mainly superficial tumours) of bladder cancer transitional cell carcinomas." *Page 26, ll. 14-20.*

The Examiner argues that Monia et al. teaches a method of detecting or quantifying the FGFR3 protein in a sample via Western blot analysis using

appropriate primary and secondary antibodies against FGFR3 protein. Monia et al. further teaches the use of antisense oligonucleotides to decrease or inhibit the expression of FGFR3 protein because "FGFs and their receptors are expressed at increased levels in several tissues and cell lines and overexpression is believed to contribute to the malignant phenotype" (see lines 31-34 on page 1 of the specification).

The Examiner relies on Cappellen et al. to teach that FGFR3b was "detected in 70 of 76 (92%) bladder carcinomas and 27 of 29 (93%) cervical carcinomas" (see page 18, right column, lines 6-18). According to the Examiner, it would have been obvious to one of ordinary skill in the art to detect the presence of bladder transitional cell carcinoma (TCC) in an individual or to assess the stage or severity of bladder TCC in an individual through the detection and/or quantification of the FGFR3b protein in a sample of an individual. Cappellen correlates the presence of FGFR3 mRNA having defined point mutations with the presence of bladder carcinoma, and teaches that because "[i]n all the samples with mutated FGFR3, FGFR3b mRNA levels were *similar to or higher than* those encountered in normal bladder and cervix epithelium."

During the Interview, we argued that Cappellen's teaching regarding mRNA levels suggests that FGFR3b levels are an unreliable way of diagnosing bladder TCC, thereby teaching away from the claimed method. Specifically, if mRNA levels of cancerous tissue are similar to those in normal tissue, mRNA levels are an

unreliable diagnostic method. The Examiner felt that the language "similar to or higher than" offered sufficient guidance to allow a skilled artisan to correlate protein expression with cancer. The Applicant respectfully disagrees with the Examiner's position that this statement offers sufficient guidance to correlate protein expression and cancer.

Further, even if the language "similar to or higher than" were to offer sufficient guidance to allow a skilled artisan to correlate protein expression with the presence of cancer, a statement that mRNA levels in cancerous or mutant tissues are *similar to or higher than* levels in normal tissue lacks sufficient specificity to allow the skilled artisan to correlate protein expression with the stage of cancer, i.e., Ta or T1 vs. T2, as in the current claims. Specifically, Cappellen fails to provide any teaching or suggestion that FGFR3 levels are higher in superficial tumors than in advanced, i.e., T2, tumors. Similarly, Monia merely links FGF overexpression to cancer; Monia fails to provide guidance on how to determine the severity of cancer based on the extent of FGF overexpression.

While we believe that the instant amendment places the application in condition for allowance, should the Examiner have any further comments or suggestions, it is respectfully requested that the Examiner telephone the undersigned attorney in order to expeditiously resolve any outstanding issues.

In the event that the fees submitted prove to be insufficient in connection with the filing of this paper, please charge our Deposit Account Number 50-0578 and please credit any excess fees to such Deposit Account.

Respectfully submitted,

KRAMER & AMADO, P.C.

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